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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/014,321	10/26/2001	Liming Shao	SPV-045.01	1490

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EXAMINER

KISHORE, GOLLAMUDI S

ART UNIT PAPER NUMBER

1615

DATE MAILED: 02/20/2004

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/014,321

Applicant(s)

SHAO, LIMING

Examiner

Gollamudi S Kishore, PhD

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 03 November 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 7-9, 12-16, 18, 20 and 23-28 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 7-9, 12-16, 18, 20 and 23-28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The RCE dated 11-3-03 is acknowledged.

The claims included in the prosecution are 1-4, 7-9, 12-16, 18, 20 and 23-28.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-4, 7-9, 12-16, 18, 20 and 23-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for fentanyl in combination with cyclodextrins, does not reasonably provide enablement for multitudes of compounds falling within the scope of the formula A in combination with micelle forming carriers and polymeric carriers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d, 1400 (Fed.Cir.1988). Among these factors are: (1) the nature of the invention; 2) the state of the prior art; 3) the relative skill of those in the art; 4) the predictability or unpredictability of the art; 5) the breadth of the claims; 6) the amount of direction or guidance presented; 7) the presence or absence of working examples; and 8) the quantity of experimentation necessary. When the above factors are weighed, it is

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the examiners position that one skilled in the art could not practice the invention without undue experimentation.

1) the nature of the invention: the invention concerns with compositions containing multitudes of compounds falling within the formula A (most of them are not even synthesized) in combination with micelle forming agents and polymeric carriers.

2) The state of the prior art: the state of the prior art is high in terms of formulating compounds with polymeric carriers and micelle forming agents.

3) The relative skill of those in the art: the skill of one of ordinary skill in the art is very high (Ph.D level technology).

4) The predictability or unpredictability in the art: although generally the activity of fentanyl or fentanyl based compounds is predictable, based on applicants themselves it would appear that there is unpredictability in the art (see applicant's response on top section of page 10 and page 7 of previous response. One would therefore, question the predictability of several of the compounds, which are not even synthesized as, would appear from instant specification.

5). The breadth of the claims: instant claim is very broad in terms multitudes of compounds, which the claimed formula A encompasses and several carriers claimed.

6) The amount of direction of guidance provided: instant specification provides no guidance at all as to how the multitudes of compounds are synthesized.

7) The presence or absence of working examples: the only example given in the specification is the oral administration of fentanyl using specific cyclodextrins

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8) The quantity of experimentation necessary: since the formula A encompasses multitudes of compounds and since generic 'polymeric carriers' and 'micelle forming agents' encompass several compounds, one of ordinary skill in the art will not be able to practice the invention without undue experimentation.

Claim Rejections - 35 USC ' 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. Claims 1-4, 7-9, 12-16, 18, 20, and 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/02256 cited before.

WO discloses cyclodextrin complexes containing fentanyl, alfentanil, sufentanil and lofentanil for the treatment of pain (note the abstract, Examples and claim 16).

WO does not teach all of the claimed compounds falling under the basic structure of fentanyl and although WO teaches only handful compounds including fentanyl, it does not provide specific example using fentanyl. However, in the absence of showing the criticality, it is deemed obvious to one of ordinary skill in the art to encapsulate

fentanyl or any compound based on the basic structure of fentanyl in the in the cyclodextrin compositions of WO with a reasonable expectation of success. WO also does not teach the method of treating pain in claimed animals. However, in the absence of showing otherwise, it is reasonable to expect that the compositions, which are effective in rats, would be effective in other animals and humans too.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants argue that one of ordinary skill in the art would not have a reasonable expectation of success in a program focused on oral administration of a formulation for the treatment of pain, which formulation comprised cyclodextrins and fentanyl or structurally related compounds. In support, applicant directs the examiner's attention to Mezei, which apparently states that the blood plasma levels of (opioids) obtained from oral preparations show wide variability. This argument is not found to be persuasive. Based on applicant's own rationale, one cannot predict the efficacy of multitudes of compounds falling under the claimed formula based on the studies of with fentanyl. A careful review of the specification indicates that the only compound tested is fentanyl and that too with a specific cyclodextrin; it is unclear to the examiner from the results on page 45 (Table) as to how one can come to any conclusion that orally administered fentanyl is effective since the comparison between saline control and the HPCD formulations show a wide variation (see columns 3 and 4 for beta-HPCD and col. 1 for gamma-HPCD).

3. Claims 1-4, 7-9, 12-16, 18, 20, and 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/36071 cited before.

WO discloses fentanyl and fentanyl derivatives in polymeric carriers (note the examples and claims).

What are lacking in WO are the teachings of the administration of the compounds to species other than humans and the administration is oral. However, it is deemed obvious to one of ordinary skill in the art to administer the composition to any animal species with the expectation of obtaining similar results since in the art of biological and medical sciences, animals are used as models for humans; mode of administration is deemed to be a manipulatable parameter and the choice of the practitioner of the art to obtain the best possible results.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants argue that the claims have been amended and that the WO reference does not teach any of the compounds that fall within the scope of claim 1. This argument is not found to be persuasive since as pointed out before, the reference teaches fentanyl and several fentanyl based compounds and therefore, one of ordinary skill in the art would be motivated to use any fentanyl based compound with a reasonable expectation of success. As also pointed out above, instant specification contains studies only with fentanyl and that too with specific cyclodextrin compounds.

4. Claims 1-4, 7-9, 12-16, 18, 20, and 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/47203 of record.

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WO teaches formulations containing narcotic analgesics such as fentanyl in combination with hydroxypropyl-beta cyclodextrin for oral administration (summary, examples and claims). Although WO does not teach all the fentanyl based compounds, it would have been obvious to one of ordinary skill in the art to use any fentanyl based compounds with a reasonable expectation of success.

5. Claims 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/02256 or WO 99/36071 cited above, further in view of Farrar et al (JNCI, 1998), Portenoy et al (Pain, 1999), Stanley et al (Anesth. Analg. 1989) by themselves (all are of record).

The teachings of WO 92 and WO 99 have been discussed above. What is lacking in these references is the oral administration of the fentanyl-based composition.

The references of Farrar et al, Porenoy et al, Stanley et al and WO each teach the efficacy of fentanyl when administered orally (note abstracts in each). The oral administration of the compositions of fentanyl based compounds, with a reasonable expectation of success would have been obvious to one of ordinary skill in the since the references of Farrar et al, Porenoy et al, Stanley et al show the efficacy of orally administered fentanyl.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, PhD whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Gollamudi S Kishore, PhD
Primary Examiner
Art Unit 1615

GSK